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# Interstitial lung diseases: characteristics at diagnosis and mortality risk assessment

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**Summary** As the diagnostic assessment of the different forms of interstitial lung disease (ILD) is similar, this study aims to compare age, sex, the functional and broncho-alveolar lavage fluid (BALF) findings at diagnosis between the different forms of ILDs. In addition we want to determine which of these variables determine survival. We evaluated 315 patients (176 males and 139 females) in whom the diagnosis was made of sarcoidosis ($n = 87$), ILD due to connective tissue disease ($n = 56$), hypersensitivity pneumonitis ($n = 50$), idiopathic pulmonary fibrosis (IPF) ($n = 64$), other forms of idiopathic interstitial pneumonia ($n = 29$) or ILD due to an undefined form of fibrosis ($n = 29$). We analysed the role on outcome of type of disease, gender, age at diagnosis, type of cells in BALF, FVC and $DL_{CO}$. In a Kaplan–Meier analysis IPF has the worst outcome in comparison with other types of ILDs. A Cox regression analysis showed that type of ILD, FVC, age at diagnosis and % of macrophages in BALF predict outcome of patients affected by ILD.


## Introduction

Interstitial lung diseases (ILD) represent a very large group of more than 200 different entities with an estimated prevalence of 74.1 per $10^5$ and incidence of $28.8 \times 10^5$ per year.[1,2]

The diagnostic assessment of the different forms of ILD is similar and is based on findings perceived on lung function, laboratory, chest-X-ray, high-resolution computed tomography, broncho-alveolar lavage fluid (BALF) and histology. Good descriptions on the assessment are available for sarcoidosis, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis (IPF) and ILD due to connective tissue disease. Furthermore for IPF, the predictive value of findings at diagnosis[3] and of the characteristics on lung biopsy has been demonstrated.[4] However, to the best of our knowledge no comparisons of possible determinants in the 6 most common forms of ILD has been published.

Clinically the different ILD's have rather similar presentations with increasing shortness of breath and widespread shadowing on the chest radiograph.[5] As the diagnostic assessment of the different forms of ILD is similar, the aim of this study was to compare the characteristics of the

*Abbreviations:* BALF, broncho-alveolar lavage fluid; CTD, connective tissue disease; $DL_{CO}$, diffusion capacity for carbon monoxide; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; SARC, sarcoidosis; TLC, total lung capacity

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different variables measured at diagnosis of the 6 most common forms of ILD entities and to determine the prognostic value of these variables on outcome.

## Methods

### Subjects

Three hundred and fifteen patients with sarcoidosis (SARC), IPF, other forms of idiopathic interstitial pneumonia (IIP), lung fibrosis due to connective tissue disease (CTD), hypersensitivity pneumonitis (HP) and undefined forms of lung fibrosis who attended the department of respiratory medicine of our hospital between 1990 and 1999 are studied. Only newly diagnosed ILD are presented in this study. These ILD-patients are registered in the framework of our prospective registration programme of ILD in Flanders,[6,7] which was approved by the local Ethical Committee. In this registration programme a standardised protocol was used for diagnostic assessment, therapy and follow-up.

### Diagnostic criteria

The diagnosis of IIP and IPF is based on criteria of the ATS-ERS consensus statements.[8,9] Our pathologist (E.V.) re-assessed the biopsies in view of the most recent classificationof the IIP.[9]

The diagnosis of sarcoidosis is based on a compatible clinical picture of multi-organ involvement, histologic demonstration of non-caseating granulomas, and exclusion of other diseases capable of producing a similar histologic or clinical picture. If clinical, broncho-alveolar lavage and/or radiological features alone are diagnostic for sarcoidosis, no biopsy is performed.[10]

All patients with connective tissue disease have a restrictive lung function defect (defined as a TLC $<$ 80%), an abnormal diffusion capacity ($DL_{CO}$ $<$ 75%) and/or the typical appearance of fibrosis and ground glass pattern on high-resolution computed tomography. The diagnosis of lupus erythemathosus disseminatus,[11] systemic sclerosis[12] and Sjögren syndrome[13] is according the criteria of the American Rheumatism Association. The criteria from Bohan et al.[14] are used for the diagnosis of dermato-polymyositis.

The diagnosis of hypersensitivity pneumonitis is based on the presence of ILD with a suggestive history and presentation[15–17] including: exposure to an agent that can induce hypersensitivity pneumonitis, shortness of breath with partial clinical and functional improvement upon avoidance of the offending agent, a restrictive lung function pattern, the presence of ground glass and/or fibrosis pattern on high-resolution computed tomography and the presence of a lymphocytosis in the BALF. If the clinical, broncho-alveolar lavage and radiological features are not convincing, a lung biopsy[18] or a specific challenge test is performed to strengthen the diagnosis of hypersensitivity pneumonitis.[19]

An undefined form of fibrosis is a lung fibrosis for which the origin or diagnosis not be defined and the findings do not match with the criteria for IIP or for other forms of ILD.

### Routine investigations in the diagnostic assessment of ILD

#### Lung function tests

Spirometry (VC, $FEV_1$) was performed with a pneumotachograph and integrator, TLC and RV were obtained by body plethysmography. CO-diffusing capacity or transferfactor ($DL_{CO}$) was measured with the single breath method. The lung function tests were performed using standard protocols, based on the guidelines and the reference values of the European Respiratory Society.[20]

#### Pulmonary histo-cytology

These investigations were performed selectively if non-invasive evaluations were not diagnostic.

BALF was generally carried out in the right middle lobe or lingula unless high-resolution computed tomography advocated an other location. Generally, $4 \times 50$ ml sterile saline was instilled and aspirated again by gentle manual suction. The recovered fluid is immediately transported to the laboratory for total and differential cell count.[21] If indicated a sampling was performed for microbiologic and for mineralogical analysis.

Generally, 4–8 peripheral transbronchiolo-alveolar biopsies (TBB) were carried out and when sarcoidosis was suspected bronchial biopsies were taken in addition.

Finally if indicated an open lung biopsy (generally 2 $cm^3$ in the middle lobe or lingula) or video-assisted thoracoscopic lung biopsies (TLB) (up to 4 biopsies from different lobes) were performed for histologic staining and microbiology.

### Statistics

All results are presented as mean (SD) values. Cox proportional hazard analysis with stepwise forward method was performed to assess the association between variables and all-cause mortality.

Univariate Cox regression analysis was completed to identify significant variables predicting survival status. Variables which were significant by univariate Cox regression analysis were taken as potential predictors of survival and were used as covariates in the forward stepwise multivariate Cox regression analysis to identify independent predictors of survival.

The relative risk ratio or hazard ratio (RR) and 95% confidence interval for risk factors are given, and Kaplan–Meier cumulative survival plots were constructed. To quantify the RR on survival between patients with or without the diagnosis of UIP the risk ratio was calculated using Cox proportional hazards analysis (with stepwise forward method). To dichotomise each value the median value of each variable was used, which made it possible to calculate the relative risk ratio. To dichotomise the variable ''diagnosis'' UIP or no-UIP is used.

The probability of death within 5 years of patients with ILD was calculated using the Kaplan–Meier method with a logistic regression analysis technique.[22]

## Results

Between 1990 and 1999 315 newly diagnosed ILD were registered for this study. An overview of diagnosis, percent biopsy proven, age and sex ratio is presented in Table 1. SARC and IIP accounted each for about 30% of the patients, CTD and HP each for about 20%. Patients with SARC were most often diagnosed in stage II. HP was by far most often found in bird fanciers, especially in pigeon breeders. Among CTD, rheumatoid arthritis and systemic lupus erythematosus were most frequent, followed by systemic sclerosis. The ILD tended in general to show a male preponderance, except for CTD. Smoking habits and therapy at diagnosis were not retained in the study.

Table 2 shows the lung function and BALF data at diagnosis for the whole group and subdivided in those who died and who survived between 1990 and 1999. The volumes (VC, TLC) and $DL_{CO}$ were lowest in IPF and highest in SARC. In general, those who died had a more restrictive lung function and a lower $DL_{CO}$, and a higher percentage of macrophages.

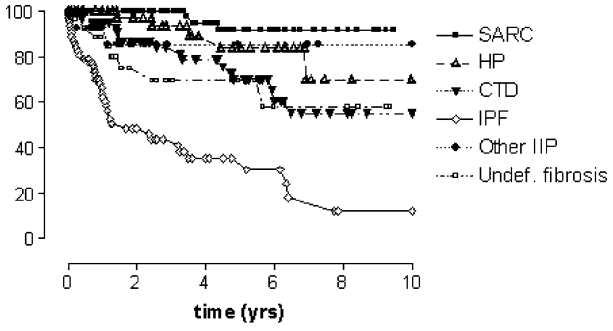
**Table 1** Overview of the different ILD and characteristics at diagnosis.

| Diagnosis | *n* | % of total | F/M | Age | % biopsy proven* |
|---|---|---|---|---|---|
| SARC | | | | | |
| Stage I | 22 | 7.0 | 1.0 | 43 (11) | 36.4 |
| Stage II | 29 | 9.2 | 0.9 | 44 (12) | 62.1 |
| Stage III–IV | 12 | 3.8 | 0.7 | 51 (14) | 41.7 |
| Not further specified | 24 | 7.6 | 0.9 | 53 (13) | 41.7 |
| Subtotal | 87 | 27.6 | 0.9 | 47 (13) | 47.1 |
| HP | | | | | |
| Bird breeder disease | 35 | 11.1 | 0.4 | 54 (16) | 28.6 |
| Other | 15 | 4.8 | 0.9 | 48 (14) | 60.0 |
| Subtotal | 50 | 15.9 | 0.5 | 52 (15) | 38.0 |
| CTD | | | | | |
| RA | 23 | 7.3 | 0.8 | 64 (12) | 17.4 |
| SLE | 13 | 4.1 | 2.3 | 40 (15) | 7.7 |
| PSS | 11 | 3.5 | 1.0 | 54 (13) | 16.7 |
| Other | 9 | 2.9 | 1.3 | 64 (10) | 33.3 |
| Subtotal | 56 | 17.8 | 1.1 | 57 (16) | 17.5 |
| IPF | | | | | |
| UIP | 64 | 20.3 | 0.5 | 65 (12) | 32.8 |
| Other IIP | | | | | |
| DIP | 12 | 3.8 | 2.0 | 51 (11) | 41.7 |
| NSIP | 7 | 2.2 | 2.5 | 63 (10) | 85.7 |
| BOOP | 10 | 3.2 | 1.5 | 55 (24) | 50.0 |
| Subtotal | 93 | 29.5 | 0.7 | 62 (14) | 39.8 |
| Undefined form of fibrosis | 29 | 9.2 | 0.9 | 65 (14) | 24.1 |
| All Total | 315 | 100.0 | 0.8 | 56 (16) | 36.1 |

*Only the biopsies that were available for review are presented.

**Table 2** Lung function and BALF data registered at diagnosis and divided in those who died and survived between 1990 and 1999.

| Outcome | Diagnosis | Lung function (% pred) | | | | BALF | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *n* | VC | TLC | $DL_{CO}$ | *n* | Cell count ($10^4$) | % Ma | % Lym | % Neu | % Eos |
| Alive | SARC | 70 | 93 (20) | 89 (20) | 79 (20) | 47 | 30 (28) | 56 (23) | 36 (24) | 7 (13) | 2 (6) |
| | HP | 43 | 84 (21) | 84 (20) | 53 (21) | 30 | 71 (70) | 37 (28) | 56 (28) | 6 (8) | 1 (2) |
| | CTD | 34 | 80 (20) | 80 (17) | 49 (20) | 16 | 38 (38) | 57 (27) | 21 (16) | 20 (22) | 2 (3) |
| | IPF | 19 | 75 (21) | 69 (17) | 41 (13) | 14 | 25 (14) | 45 (30) | 20 (21) | 27 (27) | 7 (9) |
| | IIP other | 24 | 77 (23) | 78 (18) | 46 (17) | 16 | 42 (39) | 44 (27) | 25 (18) | 2 (3) | 7 (10) |
| | Undef. fibrosis | 19 | 79 (21) | 76 (15) | 48 (22) | 14 | 37 (34) | 50 (31) | 35 (31) | 15 (21) | 2 (2) |
| Died | SARC | 2 | 87 | 81 | 44 | 3 | 23 (27) | 49 (24) | 50 (25) | 2 (1) | 3 (6) |
| | HP | 4 | 51 (12) | 67 (16) | 35 (21) | 3 | 75 | 53 (44) | 32 (40) | 16 (5) | 0 (0) |
| | CTD | 16 | 71 (16) | 66 (13) | 40 (14) | 7 | 17 (20) | 65 (27) | 26 (29) | 7 (8) | 3 (3) |
| | IPF | 33 | 61 (19) | 59 (14) | 34 (9) | 23 | 25 (19) | 67 (23) | 12 (11) | 14 (12) | 7 (9) |
| | IIP other | 3 | 60 (16) | 76 (22) | 51 (14) | 2 | 80 | 61 | 29 | 8 | 2 |
| | Undef. fibrosis | 8 | 69 (22) | 73 (21) | 44 (17) | 5 | 33 (38) | 57 (37) | 21 (31) | 22 (34) | 1 (1) |
| Total | SARC | 72 | 93 (20) | 89 (20) | 78 (20) | 50 | 29 (28) | 55 (23) | 37 (24) | 6 (12) | 2 (6) |
| | HP | 47 | 81 (22) | 83 (20) | 51 (22) | 33 | 71 (69) | 38 (29) | 53 (29) | 7 (8) | 1 (2) |
| | CTD | 50 | 77 (20) | 75 (17) | 46 (18) | 23 | 61 (94) | 59 (27) | 23 (20) | 16 (20) | 2 (2) |
| | IPF | 52 | 66 (21) | 63 (16) | 37 (11) | 37 | 25 (18) | 58 (28) | 15 (16) | 19 (20) | 7 (9) |
| | IIP other | 27 | 75 (23) | 78 (18) | 46 (17) | 18 | 40 (38) | 46 (27) | 26 (18) | 2 (2) | 6 (10) |
| | Undef. fibrosis | 27 | 76 (21) | 75 (16) | 47 (21) | 19 | 36 (34) | 52 (32) | 31 (31) | 17 (24) | 2 (2) |




| | 2 yrs | 5 yrs |
|---|---|---|
| SARC | 100.0 | 91.6 |
| HP | 97.1 | 84.1 |
| CTD | 86.3 | 69.7 |
| IPF | 48.4 | 35.4 |
| Other IIP | 85.5 | 85.5 |
| Undef.fibrosis | 74.9 | 69.5 |

**Figure 1** Kaplan–Meier analysis of the 6 different forms of ILD.

The 315 patients were followed up for a mean of 37 (33) months, 75 (23.8%) died after 0.07–116.10 months (mean 27.31 (28.33), median 14.97 months). The mean follow up period for the 240 survivors was 40.54 (34.14) months (range 0.01–137). The mean (95% confidence interval) survival time of UIP was 43.25 (30.75–55.70) months, with a median of 20.10 months, of undefined fibrosis 77.25 (57.68–96.86) months, of CTD 95.62 (79.58–111.66) months, of SARC 107.99 (101.86–114.12) months, of HP 101.50 (87.08–115.91) months and of other IIP 100.17 (82.67–117.67) months. A Kaplan Meier analysis of the 6 different forms of ILD showed significant difference in survival between the

**Table 3** Cox proportional hazards analysis of survival.

| *n* | Variable | RR | 95% CI |
|---|---|---|---|
| 315 | Age<66 yr | 0.49 | 0.30–0.79 |
| | Diagnosis of UIP | 5.21 | 3.24–8.40 |
| 275 | Age<66 yr | 0.36 | 0.20–0.65 |
| | Diagnosis of UIP | 3.35 | 1.86–6.02 |
| | % FVC<63% | 3.38 | 1.87–6.10 |
| 180 | Age<66 yr | 0.29 | 0.13–0.61 |
| | Diagnosis of UIP | 4.53 | 2.13–9.63 |
| | % Macrophages<63% | 0.38 | 0.19–0.78 |
| 180 | Age<66 yr | 0.23 | 0.12–0.46 |
| | Diagnosis of UIP | 3.26 | 1.62–6.55 |
| | % FVC<63% | 3.07 | 1.49–6.32 |
| | % Macrophages<63% | 0.39 | 0.19–0.77 |

Each variable is dichotomized using their median value as cut-off. To dichotomize the variable ''diagnosis'' the study group is divided in patients with the diagnosis of UIP (value of 1) and a group without UIP (value of 0). Since ''diagnosis of UIP'' is given the value of 1, the variable is named diagnosis of UIP. All variables presented in this table are independent from the diagnosis. The analysis is performed in four stages (see section on Results); RR, relative risk ratio, %95 CI: 95% confidence interval, UIP: usual interstitial pneumonia, FVC: forced vital capacity.

different subgroups (Fig. 1). The mean survival 2 and 5 yr after diagnosis are schematically presented (Fig. 1).

A multivariate Cox regression analysis with stepwise forward method calculated the influence on survival of diagnosis, lung function parameters, sex, age at diagnosis, BALF findings and if the diagnosis was based on lung biopsy or not. To determine the interaction between the effects of each of these variables in determining survival we evaluated two variable models: the Cox regression is analyzed with continues and with dichotomous variables.

The regression analysis with continuous variables was performed in four different stages. Taking age at diagnosis, male sex, a biopsy proven diagnosis and diagnosis (coding 1 for UIP, 2 for undefined fibrosis, 3 for CTD, 4 for SARC, 5 for HP and 6 for other IIP) into account, the risk (with 95% confidence interval) for mortality in the 315 patients with ILD was 1.02 (1.00–1.04) for age and 0.58 (0.48–0.70) for diagnosis. Taking diagnosis, age at diagnosis, male sex, FVC (% predicted), $FEV_1$ (% predicted), TLC (% predicted) and $DL_{CO}$ (% predicted) in to account, the risk for mortality in the 275 patients with ILD who received a lung function at diagnosis was 0.71 (0.57–0.87) for type of diagnosis, 0.10 (0.02–0.54) for TLC and 0.10 (0.01–0.72) for $DL_{CO}$. Taking age at diagnosis, male sex, diagnosis, total cell count, % macrophages, % lymphocytes, % neutrophils and % eosinophils in BALF into account, the risk for mortality in the 180 patients with ILD who received a BALF at diagnosis was 1.06 (1.02–1.10) for age, 0.64 (0.47–0.86) for diagnosis and 11.1 (2.54–48.48) for % macrophages.

The regression analysis with dichotomous variables is used to quantify the relative risk ratio on survival. To dichotomise each value the median value of each variable was used, which made it possible to calculate the relative risk ratio. To dichotomise the variable ''diagnosis'' UIP or no-UIP is used (Table 3). The calculation was performed using the same stepwise forward method as described above. When using the calculation with the Cox proportional hazards analysis (model with dichotomous variables), an age of less than 66 year, a diagnosis of an ILD that is not a UIP, a FVC of more than 63% predicted and a % macrophages of less than 63% in BALF indicated in this model a reduction of mortality risk (Table 3).

## Discussion

In the framework of a prospective registration programme on ILD[6,7] we compare in the present study lung function and BALF characteristics in the 5 groups that are most frequently registered, and we analyse the risk factors for mortality. We recorded 315 prevalent cases between 1990 and 1999 in our division of respiratory medicine of the

University Hospital in Leuven, i.e. sarcoidosis (SARC, 27.6%), hypersensitivity pneumonitis (HP, 15.9%), lung fibrosis due to connective tissue disease (CTD, 17.8%), idiopathic interstitial pneumonia (IIP, 29.5%) and undefined forms of fibrosis (9.2%). In agreement with other studies, our study confirms that IIP is predominantly a disease of elderly man, with a mean age of 62 years and a female to male ratio of 0.7. Patients who present with the diagnosis of sarcoidosis tend to be younger in comparison with the other ILD, and ILD due to CTD is a female disease with a female to male ratio of 1.1. The survival rates between the different forms of ILD in our study were different, with a mean survival after 5 yr of 91.6% in SARC, 84.1 in HP, 69.7% in CTD, 35.4% in IPF, 85.5% in other IIP and 69.5% in undefined forms of lung fibrosis.

The diagnosis of ILD is very complex, but these diseases have clinically similar presentations with increasing shortness of breath and shadowing on the chest radiograph.[5] The initial approach and the assessment of the diagnosis of different forms of ILD is rather similar: it involves a combination of history taking and examination of the patient, laboratory examinations, radiology (including high-resolution computed tomography of the thorax), pulmonary physiology, broncho-alveolar lavage, and histological examination. The findings in our study are interesting, because the variables used in the diagnostic assessment can be used as predictor of survival in the different ILD. We found that higher age, the type of diagnosis, the severity of functional restriction and a higher amount of percentages of macrophages in BALF are independent risk factors of mortality in the five most common forms of ILD. The finding of a diagnosis of IPF (UIP) and a FVC$<$63% predicted were the most important independent risk factor, and these findings increased the risk of mortality by more than 3 fold. The amount of macrophages in BALF and the age at diagnosis were also found to be an important risk factors for the prognosis of the disease. Gender, FVC, % lymphocytes and % neutrophils in BALF were no significant relative risk predictors.

This study has also some limitations: findings on radiology and smoking history are not included in the registration. Another limitation of this study is that not all variables could be registered in all patients: in some subjects who were referred to our out-patient clinic the values at diagnosis and the lung biopsy slides were not available for review. We found in our study a higher proportion of patients with DIP than with NSIP. A possible explanation is that a patient with DIP is more likely to be referred to our centre than a patient with NSIP, which could be a possible recruiting bias in this study.

In summary, we provided data that are derived from a large prospectively enrolled cohort showing that age, type of ILD, BALF and physiologic findings in the 5 most common forms of ILD influence prognosis.

## References


1. Coultas DB, Zumwalt R, Black W. The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med* 1994;**150**:967–72.
2. Demedts M, Wells AU, Antó JM, et al. Interstitial lung diseases: an epidemiological overview. *Eur Respir J* 2001;**18**:2s–16s.
3. King TE, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosi. Scoring system and survival model. *Am J Respir Crit Care Med* 2001;**164**:1171–81.
4. Nicholson AG, Fulford LG, Colby TV, du Bois RM, Hansell DM, Wells AU. The relationship between individual histologic features and disease progression in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2002;**166**:173–7.
5. British Thoracic Society recommendations. The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults. *Thorax* 1999;**54**:S1–S30.
6. Thomeer M, Costabel U, Rizzato G, Poletti V, Demedts M. Comparison of registries of interstitial lung diseases in three European countries. *Eur Respir J* 2001;**18**:114s–8s.
7. Thomeer M, Demedts M, Vandeurzen K. Registration of interstitial lung diseases by 20 centres of respiratory medicine in Flanders. *Acta Clin Belg* 2001;**56**:163–72.
8. ATS/ERS Committee. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med* 2000;**161**:646–64.
9. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2002;**165**:277–304.
10. ATS/ERS/WASOG Committee. Statement on sarcoidosis. *Am J Respir Crit Care Med* 1999;**160**:736–55.
11. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;**25**:1271–7.
12. Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980;**23**:581–90.
13. Fox RI, Robinson CA, Curd JG. Sjögren's syndrome. Proposed criteria for classification. *Arthritis Rheum* 1986;**29**:577–85.
14. Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med* 1975;**292**:344–7.
15. Cormier Y, Lacasse Y. Keys to the diagnosis of hypersensitivity pneumonitis: the role of serum precipitins, lung biopsy, and high-resolution computed tomography. *Clin Pulm Med* 1996;**3**:72.
16. Richerson HB, Bernstein L, Fink J, et al. Guidelines for the clinical evaluation of hypersensitivity pneumonitis. *J Allergy Clin Immunol* 1989;**84**:839–44.
17. Selman M, Chapela R, Raghu G. Hypersensitivity pneumonitis: clinical manifestations, pathogenesis, diagnosis and

therapeutic strategies. *Semin Respir Crit Care Med* 1993;**14**:353–64.
18. Coleman A, Colby TV. Histologic diagnosis of extrinsic allergic alveolitis. *Am J Surg Pathol* 1988;**12**:514–8.
19. Fink J. Hypersensitivity pneumonitis. *J Allergy Clin Immunol* 1984;**74**:1–9.
20. Official Statement of the European Respiratory Society. Standardized lung function testing. *Eur Respir J* 1993;**6**:5–100.
21. Ceuppens JL, Lacquet LM, Mariën G, Demedts M, Van Den Eeckhout A, Stevens E. Alveolar T-cell subsets in pulmonary sarcoïdosis. *Am J Respir Crit Care Med* 1984;**129**:563–8.
22. Sharma R, Florea VG, Bolger AP, et al. Wasting as an independent predictor of mortality in patients with cystic fibrosis. *Thorax* 2001;**56**:746–50.